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## Seasonal variation in sleeping metabolic rate, thyroid activity, and leptin

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**Plasqui, Guy, Arnold D. M. Kester, and Klaas R. Westerterp.** Seasonal variation in sleeping metabolic rate, thyroid activity, and leptin. *Am J Physiol Endocrinol Metab* 285: E338–E343, 2003; 10.1152/ajpendo.00488.2002.—We investigated seasonal variation in sleeping metabolic rate (SMR) and the possible relation to body composition, thyroid activity, and leptin. Twenty-five healthy volunteers were examined four times during the year: in spring (April, May), summer (July, August), autumn (October, November), and winter (January, February). Body composition was determined using a three-compartment model based on underwater weighing and the deuterium dilution method. SMR was measured during an overnight stay in a respiration chamber. A blood sample was taken for the analysis of free and total thyroxine, TSH, and leptin. SMR showed a significant seasonal variation ( $P < 0.01$ ) with a maximum in winter (4.54 kJ/min) and a minimum in summer (4.34 kJ/min). The amplitude was  $0.10 \pm 0.02$  kJ/min, and the phase was November 5th. Season explained 17% of the intraindividual variation in SMR. The circannual rhythm in SMR could not be explained by changes in body composition, thyroid activity, or leptin. Interindividual variation in SMR was explained by fat-free mass ( $P < 0.001$ ) and leptin ( $P < 0.001$ ).

body composition; thyroid-stimulating hormones; thyroxine; ambient temperature

RESTING METABOLIC RATE (RMR), determined mainly by fat-free mass (FFM), is the main component of total energy expenditure and therefore an important factor in the study of energy metabolism and obesity. One aspect influencing RMR is environmental temperature, wherein RMR is higher in a cold environment (32). Environmental temperature includes room temperature as well as ambient temperature. If ambient temperature regulates RMR, one expects a seasonal variation in RMR. Osiba (20) measured four Japanese male adults monthly under standard conditions and found a distinct seasonal variation in sleeping metabolic rate (SMR) with a summer low-winter high difference of 16.3% of the mean. Kashiwazaki (11) reanalyzed the literature on seasonal fluctuations in RMR in populations not exposed to limitations in food availability. It was stated that both indoor and outdoor temperatures at the time of measurement influenced

RMR and that seasonal influences persisted after controlling for indoor temperatures. On the contrary, a more recent study by Haggarty et al. (6) revealed no summer-winter differences in the RMR of adult males in the United Kingdom. The latter was one of the few studies including data on body composition to eliminate the possibility that the seasonal changes in RMR are due to changes in FFM.

Thyroid activity is known to be related to RMR (1, 20, 28) and is upregulated in a cold environment (4, 28), which makes it a potential regulating factor in seasonal RMR changes. Osiba (20) measured protein-bound iodine in serum as a measure of thyroxine ( $T_4$ ) content and found a seasonal variation with the peak in January. Other studies measuring free, reverse, or total triiodothyronine ( $T_3$ ), free or total  $T_4$ , or thyroid-stimulating hormone (TSH) showed contradictory results regarding seasonal influences or the moment of peak concentrations (15, 18, 24, 29).

The recently discovered hormone leptin, produced by adipocytes, could also influence RMR and has been suggested as a local autocrine/paracrine regulator of TSH release (7, 19). Very little is known about seasonal influences on leptin. Donahoo et al. (3) found no effect of season on leptin concentrations in normal-weight men and women. Perry et al. (22) found a circannual rhythm for leptin in older African American men, but the data were cross-sectional.

Despite a wide interest in seasonal variation in RMR, there are some quite contradictory results and questions to be resolved. To our knowledge, there is no study on seasonal variation in RMR, including repeated measures of SMR, body composition, and hormonal influences in both men and women, not subject to limitations in food availability. This study was designed to investigate 1) a possible seasonal variation in SMR; 2) whether or not this variation is due to a change in body composition; 3) seasonal variation in thyroid function, represented as TSH, free  $T_4$ , and total  $T_4$ , and its relation to SMR; and 4) a possible seasonal variation in leptin and its relation with SMR.

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## SUBJECTS AND METHODS

### Subjects

Subjects were 25 healthy volunteers (10 males and 15 females) between the ages of 20 and 30 yr, most of them working at the university. Detailed information about the objective and the protocol of the study was provided. Written informed consent was obtained, and the study was approved by the Ethics Committee of Maastricht University. Most subjects were working at the university, performing comparable activities. SMR, body composition, and a blood sample were obtained at subsequent time points: in spring (April, May), summer (July, August), Autumn (October, November), and winter (January, February). The subjects were not measured within 14 days before or after their vacations. Subjects' physical characteristics at baseline are shown in Table 1.

### SMR

SMR was measured during an overnight stay in a respiration chamber. The chamber measured 14 m<sup>3</sup> and was equipped with a bed, table, chair, freeze toilet, washing bowl, radio, television, and computer (26). Subjects entered the room at 2100 in the evening and left the room at 0730 in the morning. Energy expenditure was calculated from O<sub>2</sub> consumption and CO<sub>2</sub> production according to Weir's formula (33). SMR was defined as the average SMR during ≥3 h of sleep with the lowest activity measured by Doppler radar, usually between 0300 and 0600. Subjects were asked to consume their normal evening meal at home between 1800 and 1900. In order not to interfere with the subjects' normal feeding behavior and thus with energy balance, the meals were not standardized. Because SMR was measured ≥6 h, and in general 8–11 h after the meal, the effect of diet-induced thermogenesis is assumed to be minimal (27).

The respiratory quotient (RQ) was determined as a measure of substrate oxidation. Room temperature was held constant at 20 ± 1°C every season to investigate whether the seasonal effect is present when short-term effects of temperature changes are controlled for.

### Body Composition

Anthropometric measurements were taken in the morning after subjects left the respiration chamber. Body mass was measured on an electronic scale (Mettler Toledo ID1 Plus, Giessen, Germany) to the nearest 0.01 kg. Height was measured to the nearest 0.1 cm (SECA Mod.220, Hamburg, Germany). Body volume was measured by underwater weighing. Residual lung volume was simultaneously measured with the helium dilution technique. Total body water (TBW) was measured by deuterium dilution according to the Maastricht protocol (34).

Body composition was calculated from body density and TBW using Siri's three-compartment model (30).

Table 1. Subjects' characteristics at baseline

	Women	Men
<i>n</i>	15	10
Age, yr	25 ± 2	26 ± 2
Height, m	1.72 ± 0.07	1.82 ± 0.08
Body mass, kg	64.4 ± 5.9	69.2 ± 9.6
BMI, kg/m <sup>2</sup>	21.9 ± 1.9	20.9 ± 2.0
Body fat, %	26.1 ± 5.5	15.7 ± 3.4

Values are means ± SD. BMI, body mass index.

### Blood Sample

After the anthropometric measurements and before the consumption of any food or drinks, a blood sample was taken for the analysis of leptin, total T<sub>4</sub>, free T<sub>4</sub>, and TSH.

### Ambient Temperature

Data on 24-h average ambient temperature were supplied by the Royal Dutch Meteorological Institute and were collected at a location near the university (Maastricht, Beek; 51° North, 6° East).

### Statistics

All variables were tested for normal distribution and were log transformed if necessary. A general sinusoidal model was used to investigate a within-subjects seasonal variation in SMR and hormone levels

$$Y = c + A \cdot \sin[(d - d_0)/365 \cdot 2\pi]$$

or

$$Y = c + \underbrace{A \cdot \cos(2\pi d_0/365)}_{b_1} \cdot \underbrace{\sin(2\pi d/365)}_{X_1} - \underbrace{A \cdot \sin(2\pi d_0/365)}_{b_2} \cdot \underbrace{\cos(2\pi d/365)}_{X_2}$$

where *c* is a constant, *A* is the amplitude, *d* is day of the year the measurement was done, and *d*<sub>0</sub> is the phase. ANOVA was used to determine *b*<sub>1</sub> and *b*<sub>2</sub>, and an *F*-test was used to determine the significance of the sinusoidal model. The amplitude and the phase were then calculated as

$$A = (b_1^2 + b_2^2)^{1/2}$$

and

$$d_0 = 365/2\pi \cdot \arccos(b_1/A)$$

To correct for the menstrual cycle, the phase of the menstrual cycle was put into the model. Measurements for women in the postovulation phase were coded 1, whereas those for men and for women in the preovulation phase were coded 0.

A multiple regression analysis with a backward-selection procedure was performed to identify the determinants of interindividual variation in SMR. All analyses were done with SPSS 10.0 for Macintosh (SPSS, Chicago, IL) and Statview 5.0 for Macintosh (SAS Institute, Cary, NC). The statistical significance level was set at *P* < 0.05.

## RESULTS

### Seasonal Variation

**SMR and FFM.** Mean values for SMR and FFM for men and women in each season are presented in Table 2. There were no significant differences in FFM over the year either for women or for men.

SMR showed a significant seasonal variation, with a summer minimum (August) winter maximum (February) (*P* < 0.01). Figure 1 shows mean SMR in the four seasons and the calculated sinusoidal curve. The mean value over the year was 4.44 ± 0.50 kJ/min, the amplitude was 0.10 ± 0.02 kJ/min (2.2 ± 0.5%), and the phase was November 5th. Mean SMR over the year

Table 2. Average ambient temperature, SMR, FFM, FM, TSH, total  $T_4$ , free  $T_4$ , and leptin in different seasons

	Spring	Summer	Autumn	Winter
Ambient temperature, °C	11 ± 4	21 ± 3	8 ± 4	6 ± 3
Men				
SMR, kJ/min	4.80 ± 0.70	4.56 ± 0.53	4.72 ± 0.58	4.85 ± 0.55
FFM, kg	58.4 ± 8.6	58.6 ± 7.6	58.2 ± 8.4	58.5 ± 8.3
FM, kg	10.8 ± 2.6	10.5 ± 4.3	10.7 ± 3.5	11.4 ± 3.1
TSH, mU/l	1.4 ± 0.6	1.7 ± 1.3	1.3 ± 0.7	1.2 ± 0.5
Total $T_4$ , nmol/l	104 ± 11	105 ± 15	108 ± 12	101 ± 9
Free $T_4$ , pmol/l	13.8 ± 1.6	14.0 ± 1.0	14.2 ± 1.9	13.1 ± 1.1
Leptin, ng/ml	2.5 ± 1.2	2.5 ± 0.8	2.3 ± 0.6	2.6 ± 1.0
Women				
SMR, kJ/min	4.27 ± 0.28	4.14 ± 0.30	4.31 ± 0.38	4.29 ± 0.29
FFM, kg	47.5 ± 4.3	47.4 ± 4.5	47.3 ± 4.4	47.7 ± 4.4
FM, kg	17.0 ± 4.4	17.3 ± 4.1	17.4 ± 4.2	17.1 ± 4.7
TSH, mU/l	1.9 ± 0.8	2.0 ± 0.8	1.9 ± 1.0	1.7 ± 0.5
Total $T_4$ , nmol/l	112 ± 17	116 ± 22	112 ± 18	111 ± 23
Free $T_4$ , pmol/l	12.6 ± 2.1	12.1 ± 1.9	12.2 ± 1.4	12.6 ± 2.0
Leptin, ng/ml	11.2 ± 5.6	10.4 ± 5.5	13.2 ± 7.2	11.5 ± 6.7

Results are presented as means ± SD. SMR, sleeping metabolic rate; FFM, fat-free mass; FM, fat mass; TSH, thyroid-stimulating hormone;  $T_4$ , thyroxine.

was lower for women ( $4.25 \pm 0.29$  kJ/min) than for men ( $4.73 \pm 0.58$  kJ/min;  $P = 0.01$ ), but the amplitude ( $0.08 \pm 0.03$  kJ/min or  $1.9 \pm 0.7\%$  for women vs.  $0.14 \pm 0.04$  kJ/min or  $3.0 \pm 0.8\%$  for men) and the phase (October 13th for women, November 25th for men) were not significantly different between the sexes. There was no significant effect of the menstrual cycle on SMR over the year.

Figure 1 also shows the mean ambient temperature for each season and the sinusoidal curve for ambient temperature over the year. The seasonal pattern in ambient temperature was almost the exact opposite of the pattern in SMR, and the descending part of the temperature curve crossed the mesor (average value over the year) 1 wk before the phase of the SMR curve, suggesting a causal relationship.

Overnight, the RQ, as a measure of substrate oxidation, was not significantly different between seasons, being  $0.83 \pm 0.03$  in spring,  $0.84 \pm 0.04$  in summer,  $0.81 \pm 0.04$  in autumn, and  $0.82 \pm 0.03$  in winter.

**Thyroid activity.** Mean values ± SD for women and men separately for each season are summarized in

Table 2. With both men and women taken together, no seasonal variation in free  $T_4$ , total  $T_4$ , or natural logarithm of TSH [ln(TSH)] was observed. With men and women analyzed separately, a significant seasonal variation in free  $T_4$  was observed for men ( $P < 0.05$ ). The amplitude was  $0.49 \pm 0.18$  pmol/l ( $3.6 \pm 1.3\%$ ), and the phase was November 6th. The seasonal variation in free  $T_4$  was not related to SMR. In women, there were no seasonal effects.

**Leptin.** Mean values ± SD for men and women for each season are presented in Table 2. There was no seasonal variation in ln(leptin) for women or for men.

*Determinants of SMR*

**Intraindividual variation.** For women and men together, season explained 17% of the intraindividual variation in SMR over the year (12% for women and 25% for men). Ambient temperature also explained 17% and made the seasonal effect disappear. None of the measured hormones contributed significantly to the explanation of the seasonal variation in SMR. However, in men, there was an additional effect of total  $T_4$ , which was negatively correlated with SMR and explained another 8% of the intraindividual variation in SMR.

**Interindividual variation.** To explain interindividual variation in SMR, average values of the four repeated measures were used in a multiple regression analysis with SMR as the dependent variable and sex, FFM, fat mass (FM), total  $T_4$ , free  $T_4$ , ln(TSH), and ln(leptin) as the independent variables. Only FFM ( $P < 0.001$ ) and ln(leptin) ( $P < 0.001$ ) were significant predictors of SMR ( $R^2 = 0.91$ ). Coefficients, significance levels, partial and semipartial correlations, and  $R^2$  values of the model are presented in Table 3.

**DISCUSSION**

The results show a seasonal variation in SMR with a minimum in summer and a maximum in winter. The

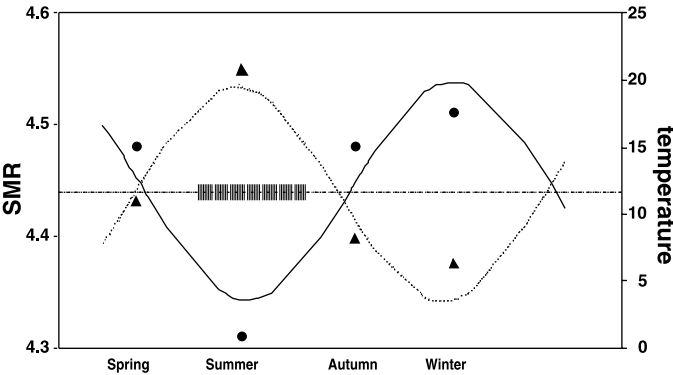


Fig. 1. Sinusoidal curve of sleeping metabolic rate (SMR; kJ/min; solid line) and ambient temperature (°C; dashed line) and average values for each season for SMR (●) and ambient temperature (▲). For calculation of sinusoidal curves see METHODS, Statistics.



Table 3. *Significant predictors of SMR*

	Coefficients	SE	P	Partial R	Part R	R <sup>2</sup> (model)
Constant	0.58	0.31	0.079			0.91
FFM	$6.75 \times 10^{-2}$	$0.50 \times 10^{-2}$	<0.001	0.95	0.88	
ln(Leptin)	0.21	0.05	<0.001	0.69	0.28	

Significant predictors of SMR, determined by stepwise regression analysis using backward selection, with SMR as the dependent variable and sex, FFM, FM, total T<sub>4</sub>, free T<sub>4</sub>, natural logarithm (ln) ln(TSH), and ln(leptin) as independent variables: coefficients, standard error (SE), significance (P), partial (partial R) and semipartial correlation (part R), and R<sup>2</sup> of the model.

seasonal changes were not due to changes in FFM or any of the measured hormones. In men, there was a significant seasonal variation in free T<sub>4</sub> that was not related to SMR, whereas total T<sub>4</sub> did not show a seasonal pattern but did explain an additional 8% of the intraindividual variation in SMR. FFM and leptin rather than FM explained between-subject variation in SMR.

The seasonal variation in SMR was highly significant ( $P < 0.01$ ), with an amplitude of 0.10 kJ/min, or 2.3% of the mean, for women and men together. The summer low-winter high difference was two times the amplitude, or 4.5% of the mean. There was a difference in ambient temperature of 15°C between summer and winter (Table 2). Kashiwazaki (11) calculated that, at a constant room temperature of 20°C, which was the case in this study, an increase in ambient temperature from 5 to 20°C would cause a drop in basal metabolic rate (BMR) of 4.2% for an average male subject (1.68 m, 65 kg, 40 yr). His calculation was based on data on 123 subjects from six different studies and is very close to the results found in this study. Osiba (20) calculated a change of 6.6% in BMR per 10°C on the basis of the data from nine Japanese males. He also found a higher BMR in spring than in autumn despite the same environmental temperature and suggested that it takes some time for the adaptive changes in BMR to take place. In this study, no significant differences in SMR between spring and autumn were found, but there were indications of a direct relationship between environmental temperature and SMR. Season and ambient temperature each explained the same amount of variation in SMR within subjects. Furthermore, the descending part of the temperature curve crossed the mesor 1 wk before the phase of the SMR curve; in other words, the SMR curve lagged 1 wk behind the temperature curve. These results suggest that ambient temperature has a long-term metabolic effect.

Understanding of the mechanism behind these adaptive changes in SMR to season is still incomplete. Thyroid activity is known to be upregulated in a cold environment, but it is not clear whether this is caused by the drop in temperature itself or to increased food intake as a result of the cold exposure (4, 5, 9, 31). Furthermore, increased thyroid activity is able to increase basal metabolism (28), which makes the thyroid gland a possible regulator for seasonal changes in SMR. Studies on seasonal changes in thyroid hormones showed contradictory results. Seasonal variations in T<sub>3</sub> and/or T<sub>4</sub> (13, 15, 21) have been documented by some

authors but contradicted by others (24). TSH was found to be higher in winter in middle-aged and older men and women (29) and in hyperthyroid patients treated with T<sub>4</sub> (12) but not in young adults (29). Our data showed a seasonal variation in free T<sub>4</sub> for men only. TSH and total T<sub>4</sub> did not change significantly over the year either for women or for men. However, the seasonal variation in free T<sub>4</sub> did not explain the observed seasonal trend in SMR. Total T<sub>4</sub> did not show a seasonal pattern but was negatively correlated with SMR and explained an additional 8% of the intraindividual variation in SMR in men. The negative correlation might be due to a high turnover from T<sub>4</sub> into T<sub>3</sub>, the metabolically active form of T<sub>4</sub>. Osiba (20) combined his measures of serum protein-bound iodine with measures of BMR and found peak values for both in winter, which might indicate a causal relationship. He stated that the correlation between protein-bound iodine and BMR was 0.77. However, he based his equation on the data of four persons each measured 12 times. Thus he included both intra- and intervariability in the regression analysis, which might lead to the wrong conclusion that the seasonal variation in BMR is due to changes in thyroid activity. Konno and Morikawa (12) found higher TSH concentrations in winter than in summer but that BMR remained unchanged. The fact that we did not find a significant relation between thyroid hormones and seasonal BMR changes does not necessarily mean that there is none. Blood levels of TSH display diurnal variation with a nocturnal rise. Despite the fact that the blood sample was taken at approximately the same time in the morning each season, a more continuous sampling might be recommended.

This is the first study to investigate leptin in relation to seasonal changes in RMR. There was no seasonal variation in leptin, and leptin was not related to the circannual rhythm in SMR. However, linear regression revealed FFM and leptin as the significant determinants of between-subject variation in SMR. Studies investigating the relationship between leptin and RMR showed contradictory results. Mackintosh and Hirsch (14) found no effect of leptin administration on RMR in normal-weight men. Hukshorn et al. (8) treated obese subjects with pegylated recombinant native human leptin (PEG-OB) or placebo, both in combination with a hypocaloric diet, and found no differences in  $\Delta$ RMR (pre- and postintervention) between groups. Some studies found a positive relationship between RMR and leptin, but no corrections for FM were made (10, 17).

When both FFM and FM were corrected for, no correlation (16, 25), or even a negative correlation, was found (2). A positive correlation was found in anorectic subjects, in whom leptin was suggested to play a role in the energy-sparing response to exposure to chronic energy deficiency (23). Despite the difficulty in comparing the different studies because of the wide variety in sex, age, and body mass index of the study populations and the different approaches to correct for FFM and/or FM, the general conclusion seems to be that leptin is not related to RMR when subjects are in energy balance. We used a stepwise regression approach and found that, after FFM ( $P < 0.001$ ), leptin ( $P < 0.001$ ) was a stronger predictor of RMR than FM ( $P =$  not significant), resulting in a prediction of 91% of RMR. This indicates that, in this population of normal-weight males and females, leptin is an important factor in the regulation of resting energy expenditure.

To our knowledge, this is the first study to investigate seasonal variation in RMR including both an accurate measurement of body composition and hormonal influences in both men and women. The study provides additional proof of an upregulation of RMR in winter. This supports the theory of an energy-producing mechanism as a protection against cold, even in the long term. We were unable to demonstrate a relationship of these seasonal SMR changes to activity of the thyroid gland. We took a single blood sample in the morning for the analysis of free and total  $T_4$  and TSH as a measure of thyroid function. Perhaps a more frequent and/or continuous sampling would provide a better picture of thyroid activity. Furthermore, other hormones, such as sex steroids or melatonin, might be important and interesting to investigate. Another possibility is to include measurements of body temperature. Current technologies allow accurate registration of rectal and/or intestinal temperature over 24 h or even longer.

We were unable to reveal the mechanism behind seasonal RMR changes, which makes it an interesting topic for future research. When doing so, it is, in our opinion, crucial to include an accurate measurement of body composition.

In conclusion, we found a distinct seasonal variation in SMR for both men and women, possibly triggered by environmental temperature. Furthermore, FFM and leptin were the only predictors of between-subject variability in SMR, indicating an important role for leptin in the regulation of RMR.

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